IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

CESAR MILSTEIN ET AL.

Group No.: Unknown

Examiner: Unknown

Serial No.: 10/506, 906

Filed: September 7, 2004
(International Filing Date: March 7, 2003)

Title: SCD FINGERPRINTS

Attorney Docket No.: DYC 0101 PUSA

PETITION TO MAKE SPECIAL
FOR NEW APPLICATION

Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to M.P.E.P. § 708.02, VIII and X, Applicants hereby petition to make this new application special, further noting that the application has yet to be examined. Our method of sCD antigen fingerprinting body fluids should help with the diagnosis and monitoring of treatment in HIV, AIDS and cancer. All three of these pathological processes result in perturbations of immune system function, and as such result in altered patterns of soluble CD antigen expressions.

All the claims in this case are believed to be directed to a single invention. If the Office determines that all the claims presented are not obviously directed to a single invention, then Applicants will make an election without traverse as a prerequisite to the grant of special status.

A search has been made by the inventors and a foreign patent office in the following:

Field of search:	435 - Molecular Biology 436 - Immunological Testing 707 - Data Processing
Class(es)/Subclass(es):	435/4, 7.1 436/517, 819 707/100, 104.1
Publications:	See International Search Report, Information Disclosure Statement PTO/SB/08B and Application Appendix I for references.
Patents:	None

There are submitted herewith a copy of the references deemed most closely related to the subject matter encompassed by the claims. Each of the non-patent literature references are cited in the attached International Search Report. There were no patents, foreign or domestic, identified in the International Search Report. An Information Disclosure Statement was filed March 24, 2005 containing the International Search Report non-patent literature references. Two additional non-patent literature reference were identified in the review of the International Search Report references and are the basis of the IDS filed with the Petition to Make Special.

In addition, submitted herewith is a detailed discussion of the references which describe how the claimed subject matter is distinguishable over the references.

Review of Claims Over Prior Art

Claims 25-48 are pending in the present application. Claims 25, 29, 35, 36, 37, 38, 39, 41, and 43 are independent claims.

The present invention provides methodology in which multiple sCDs are simultaneously analyzed to produce a fingerprint. The fingerprint is then advantageously used to facilitate diagnosis and/or prognosis of a disease. Characteristically, the sCDs evaluated by the present invention may not be unique in their presence, absence, elevation or depression in a particular disease state. Indeed, numerous different disease states may possess numerous similar or identical individual sCD results. Clearly, by applying the prior art techniques of biomarker assay, these disease states could never be successfully distinguished. However, the present invention advantageously permits such disease states to be discriminated. This is due to the simultaneous analysis of a minimum of five different sCDs in production of the fingerprint. It is this 'parallel processing' which is both novel and inventive with regard to the state of the prior art. Furthermore, it is this feature which brings the technical advantages associated with the sCD fingerprint database. Table 1 provides an evaluation in summary fashion of the distinguishing features of the present invention over the prior art. The table is followed by a detailed summary of the prior art references and discussion of the independent claims of the present invention.

Table 1. Reference Evaluation.

No.	Author	Disease State	sCD molecule (marker)/ Body Fluid	Findings	Comment
1	Biglino, A., et al	HIV and EBV (IM)	sCD8 (T-cell surface antigen) /serum	Increased in HIV-1 and EBV patients	Use of one sCD molecule as biomarker; does not contemplate sCD fingerprint of 5 or more sCDs.
2	Osmond, D.H., et al	AIDS	sCD8 (T-cell surface antigen) /serum	Increased in AIDS patients	Use of one sCD molecule as biomarker; does not contemplate sCD fingerprint of 5 or more sCDs.

No.	Author	Disease State	sCD molecule (marker)/ Body Fluid	Findings	Comment
3	De Milito, A., et al	HIV	sCD27 (T-cell activation antigen)/plasma	Increased in HIV-1 patients	Use of one sCD molecule as biomarker; does not contemplate sCD fingerprint of 5 or more sCDs.
4	Swaak, A.J.G., et al	SLE	sCD25 (IL-2 receptor) /serum sCD27 (T-cell activation antigen) /serum	Increased Increased	Use of two sCD molecules as biomarkers found correlation with disease. **Note:** sCD27 overlaps HIV-1, an unrelated disease state. Confirming more than 2 sCDs would be required for a diagnostic profile or fingerprint for any disease state.
5	Ribbens, C., et al	RA	sCD23(IgE receptor) /synovial fluid sCD25 (IL-2 receptor) /synovial fluid	Increased Increased	Use of two sCD molecules as biomarkers found correlation with disease. **Note:** sCD25 overlaps SLE, an unrelated disease state.
6	Knauf, W.U., et al	B-CLL	sCD23 (IgE receptor) /serum sCD25 (IL-2 receptor)/serum	Increased Increased	Use of two sCD molecules as biomarkers found correlation with disease. **Note:** Both sCDs overlap two unrelated disease states (sCD23-RA and sCD25 with RA and SLE).

Reference No. 1: "Serum Cytokine Profiles in Acute Primary HIV-1 Infection and in Infectious Mononucleosis" by Biglino et al. in Turin, Italy was a study "to compare the immune activation patterns [not disease progression] of acute primary HIV-1 and EBV infections." The selected serum cytokines included indicators of macrophage activation, T-lymphocyte activation and T-suppressor/cytotoxic cell activation. The only sCD monitored

was sCD8 a T-suppressor/cytotoxic cell biomarker. Both disease states showed higher sCD8 levels compared to controls. The authors were able to demonstrate the sCD8 increases and remains higher than control and EBV which increases and then decreases over time. "In both clinical situations, peripheral blood CD8+ cell counts as well as serum sCD8 levels appeared to be positively correlated with macrophage activation products."

Reference No. 2: "Immune activation markers and AIDS prognosis" by Osmond et al. in San Francisco, California, evaluated the use of four assays of celluar products as prognostic markers for AIDS. The authors, in a prospective study of HIV-seropositive homosexual men, followed for 36 months of follow-up, determined that the sCD8 levels along with neopterin, beta 2-microglobulin and IL-2 receptor showed a correlation with immune activation. Specifically, the authors determined that for a given CD4 cell count range, it was possible to use an immune activation marker in combination with a p24 antigen assay to determine those who may be a low risk or a high risk of developing AIDS. The authors, however, limit their findings to those patients with a CD4 count of between 200-499 x 10(6) cells/l.

Reference No. 3: "Plasma levels of soluble CD27: a simple marker to monitor immune activation during potent antiretroviral therapy in HIV-1-infected subjects" by De Milito et al. in Siena, Italy, was a study undertaken "to evaluate the possibility of using the plasma levels of sCD27 as a marker for therapy monitoring in a cohort of HIV-1-infected patients undergoing highly active antiretroviral therapy [HAART]." The study selected a single sCD, sCD27 (T-cell activation antigen from the TNF receptor superfamily) and neopterin, a soluble biomarker for immune system activation. Their findings show only baseline sCD27 levels were predictive of an increase in CD4+ T-cell counts. Discontinuation of therapy resulted in a rapid rise in sCD27 and rebound of viraemia and drop in CD4+ T-cell count. The authors suggest that sCD27 may be a simple marker to monitor immune activation [not disease progression] during antiretroviral therapy.

Reference No. 4: "Serum Levels of Soluble Forms of T Cell Activation Antigens CD27 and CD25 in Systemic Lupus Erythematosus in Relation with Lymphocytes Count and Disease Course" by Swaak et al. in The Netherlands, evaluated "profiles of both T-cell activation markers (sCD25 and sCD27) in relationship to each other and to the disease course in three SLE patients." They also performed a longitutinal study of "the interrelationship between the profiles of sCD25 (IL-2 receptor alpha subunit) and sCD27 (T-cell activation antigen) with regard to lymphocyte levels. A cross-sectional study was also performed with 69 SLE patients with defined clinical symptoms. The T-cell activation markers chosen for the study demonstrated a correlation of T-cell activation before and during exacerbation and decline thereafter." However, the authors admit that "between the separate levels no correlation could be calculated, but between disease course and the lymphocyte (cell) count in most instances a relationship was shown."

Reference No. 5: "Increased synovial fluid (SF) levels of soluble CD23 are associated with an erosive status in rheumatoid arthritis (RA)" by Ribbens et al. in Liege, Belgium, was an examination of sCD23 (low affinity IgE Fc receptor) and sCD25 (IL-2 receptor alpha subunit) levels in the SF of RA patients and compared subpopulations matched for disease duration but differing by the presence or absence of x-ray erosions." They also analyzed cytokines which participate in the RA immune process. Although they found elevated SF levels of sCD23 "to be specific of an erosive behaviour of RA but also to be present before erosions are x-ray diagnosed." The authors believe they have demonstrated that SF sCD23 may be a parameter of predictive value for joint destruction. A review of the data shows the responses for the two biomarkers do overlap for the subgroups.

Reference No. 6: "Serum Levels of Soluble CD23, but not Soluble CD25, Predict Disease Progression in Early Stage B-Cell Chronic Lymphocytic Leukemia" by Knauf et al. in Augsburg, Germany, was a prospective examination of "sCD23 and sCD25 as risk factors for disease progression in early stage B-CLL." A correlation between the levels of these two biomarkers and with the stages of B-CLL was previously established. The authors found "[t]he predictive power of the sCD23 levels seems to be of greater value than their significance during the follow-up of the disease. Despite the fact that some individual patients

exhibited increasing levels of sCD23 at the time of disease progression, the difference was not of statistical evidence in the whole group of the 20 patients analyzed. This also held true for the sCD levels, but, due to the small number of patients studied during follow-up, the relavance of sCD23 and of sCD25 in patient monitoring remains to be further examined."

The non-patent literature in general recite the use of soluble biomarkers to find correlations to disease progression, immune system activation, and exacerbation of physical symptoms for previously diagnosed patients. It is also important to note that while several references describe a simple marker for use in their specific disease state, a comparison of the literature shows the same biomarkers elicit the same response in unrelated disease states.

Claim 25 discloses a shed Cluster of Differentiation (sCD) fingerprints that include levels of five or more sCDs which represent one or more disease states. Although the prior art references 1 through 6 contemplate the use of the sCD molecules as biomarkers of certain diseases, none of the references discloses sCD levels measured to "five or more sCDs" for "one or more disease states" as required by claim 25. Instead, these references provide the utilization of one or two sCDs measured in patients with a particular disease state.

Claim 29 discloses a method of generating a sCD fingerprint by measuring the levels of "five or more sCDs". Prior art Reference Nos. 1-6 only identify the use of the sCD measurements of one or two sCDs. For example, Swaak et al. (Reference No. 4) discloses a study which evaluates "T-cell activation markers (sCD25 and sCD27) in relation to each other, and to the disease course in three SLE patients". The authors found proof that active recruitment of unprimed T-cells takes place. Ribbens et al. (Reference No. 5) and Knauf et al. (Reference No. 6) found, similar to Swaak et al. (Reference No. 4), the same sCD25 biomarker and sCD23 increased in patients with Rheumatoid Arthritis and B-Cell Chronic Lymphocytic Leukemia. None of the cited references appreciate the utilization of "five or more sCDs" for "one or more disease states", as required by claim 29.

Claim 35 discloses a method for predicting the presence of one or more disease states. The method of this claim involves comparing one or more sCD fingerprints generated

from that individual with one or more reference sCD fingerprints. The prior art references (Reference Nos. 1-6) generally evaluated patients already clinically diagnosed and thus the use of the biomarkers was not intended to be diagnostic. Osmond et al. in 1991 (Reference No. 2) set out to predict whether patients who are HIV seropositive would develop AIDS. However, the sCD8 was one of four serum markers which when combined with a specific range for the CD4 count and included a test for p24 could segregate those patients at low and high risk for developing AIDS. Although a prospective study, the study utilized only one sCD molecule, along with other immune activation markers and the patients were all HIV seropositive and so the results are expected. Accordingly, none of the references disclose the step of comparing sCD fingerprints generated from an individual with one or more reference sCD fingerprints to detect the presence of one or more disease states, as required by claim 35.

Claim 36 discloses a method for detecting the extent of one or more disease states in an individual. Claim 36 provides for the evaluation of more than one disease state in an individual by generating a sCD fingerprint to be compared to several different reference sCD's of various disease states. Characteristically, the sCD fingerprint includes levels of five or more sCDs wherein the sCD fingerprint represents one or more disease states. The prior art (Reference Nos. 1-6) is limited to detection of one or two biomarkers for one disease and the status of the one or two biomarkers selected. The prior art in general relates to one disease state only. Specifically Biglino et al. (Reference No. 1) compares the levels of sCD8 in two sets of patients with HIV and EBV (mononucleosis) and finds an elevation in both sets of patients. But Biglino does not contemplate evaluation of one patient with both diseases. None of the prior art references contemplates using sCD fingerprints having "levels of five or more sCDs", as required by claim 36.

Claim 37 discloses a method for assessing the progression of a disease state by comparison with an sCD fingerprint taken at different time periods during the occurrence of the disease state. Characteristically, the sCD fingerprint includes levels of five or more sCDs wherein the sCD fingerprint represents one or more disease states. The prior art (Reference Nos. 1-6) is limited to detection of one or two biomarkers for one disease and the status of the one or two biomarkers selected. Claim 37 is further distinguished from the prior art as

follows: DeMilito et al. (Reference No. 3) studied the use of sCD27 and neopterin as biomarkers having prognostic significance for disease progression based on subgroup analysis of HIV patients. DeMilito suggests that sCD27 may be an alternative marker to monitor immune activation [not progression of disease state]. The present invention, although inclusive of immunological disease states is also novel for progression of non-immunological disease states wherein the sCD is not complicated by immune incompetence. However, as set forth above, the prior art (Reference Nos. 1-6) is limited to detection of one or two biomarkers for one disease and the status of the one or two biomarkers selected. Again, none of the prior art references contemplate using sCD fingerprints having "levels of five or more sCDs" as required by claim 36.

Claim 38 discloses a method for assessing the effect of one or more therapeutic or potentially therapeutic agents. The use of the sCD fingerprint to monitor the individuals sCD status during treatment with agents of proven therapeutic effectiveness or potentially therapeutic experimental agents. Characteristically, the sCD fingerprint includes levels of five or more sCDs wherein the sCD fingerprint represents one or more disease states. The prior art (Reference Nos. 1-6) is limited to detection of one or two biomarkers for one disease and the status of the one or two biomarkers selected. The present invention is further distinguished from DeMilito (Reference No. 3) which suggests sCD27 may be a simple marker to monitor immune activation during therapy. DeMilito et al. combined with the prior art, does not contemplate an sCD fingerprint comprised of five or more sCD levels, to evaluate therapy Again, none of the prior art references contemplate using sCD fingerprints having "levels of five or more sCDs", as required by claim 38.

Claim 39 discloses a method for assessing the effect of interventions on an individual. Characteristically, the sCD fingerprint includes levels of five or more sCDs wherein the sCD fingerprint represents one or more disease states. The prior art (Reference Nos. 1-6) is limited to detection of one or two biomarkers for one disease and the status of the one or two biomarkers selected. The prior art (Reference Nos. 1-6) does not describe a method for assessing the effect of the interventions described in the present invention. Although, DeMilito et al. (Reference No. 3) does describe conventional anti-retroviral therapy

which may be considered a type of chemotherapy, neither DeMilito et al. nor any of the other prior art references disclose an sCD fingerprint comprising five or more sCDs.

Claim 41 discloses a method for sorting the sCD fingerprints first using the sCD response level and then one or more clinical characteristics. The prior art (Reference Nos. 1-6) does not disclose sub-categorizing sCD fingerprints by sCD levels that exhibit common characteristics.

Claim 43 discloses an sCD database containing the sCD fingerprints of patients with various disease states and normal sCD fingerprints for reference. This database envisions the use of a system of entering the sCD fingerprint data for retrieval and comparison of sCD fingerprints. The prior art (Reference Nos. 1-6) do not describe a database of sCD fingerprints.

Accordingly, since independent claims 25, 29, 35-39, 41 and 43 are patentable over the prior art, dependent claims 26-28, 30-34, 40, 42 and 44-48 are also patentable.

The $130.00 fee under 37 C.F.R. § 1.17(h) is being made herewith. The Commissioner is authorized to charge any additional fees or credit any overpayment as a result of filing this paper to Deposit Account No. 02-3978.

Respectfully submitted,

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INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 03/00974

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/68 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WOOLFSON A ET AL: "ALTERNATIVE SPLICING GENERATES SECRETORY ISOFORMS OF HUMAN CD1" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 91, no. 14, July 1994 (1994-07), pages 6683-6687, XP001152660 ISSN: 0027-8424 the whole document --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2003	11/07/2003

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 03/00974

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SWAAK A J G ET AL: "Serum levels of soluble forms of T cell activation antigens CD27 and CD25 in systemic lupus erythematosus in relation with lymphocytes count and disease course." CLINICAL RHEUMATOLOGY, vol. 14, no. 3, 1995, pages 293-300, XP009011883 ISSN: 0770-3198	1-17
Y	the whole document	1-24
X	BIGLINO, A. ET AL: "Serum cytokine profiles in acute primary HIV-1 infection and in infectious mononucleosis" CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, vol. 78, no. 1, January 1996 (1996-01), pages 61-69, XP002245772	1-17
Y	the whole document	1-24
X	KNAUF W U ET AL: "SERUM LEVELS OF SOLUBLE CD23, BUT NOT SOLUBLE CD25, PREDICT DISEASE PROGRESSION IN EARLY STAGE B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA" LEUKEMIA AND LYMPHOMA, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 27, no. 5/6, 1997, pages 523-532, XP009011890 ISSN: 1042-8194	1-17
Y	the whole document	1-24
X	RIBBENS C ET AL: "Increased synovial fluid levels of soluble CD23 are associated with an erosive status in rheumatoid arthritis (RA)." CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 120, no. 1, April 2000 (2000-04), pages 194-199, XP009011870 ISSN: 0009-9104	1-6,8-17
Y	the whole document	1-24